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氯吡格雷用于缺血性脑卒中的疗效评价及对血小板活性及血清炎症因子水平的影响*

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摘要 目的:评价氯吡格雷用于缺血性脑卒中的疗效及对血小板活性及血清炎症因子水平的影响。**方法:**选择我院 2016 年 8 月~2018 年 8 月收治的 150 例缺血性脑卒中患者,按入院先后顺序分为对照组(83 例)和研究组(67 例)。对照组采用常规治疗,研究组在对照组基础上联合氯吡格雷治疗，比较两组的临床疗效，治疗前后血小板活性指标，血清超敏 -C 反应蛋白(hypersensitive c-reactive protein,hs-CRP)、白介素 -6(Interleukin-6,IL-6)及肿瘤坏死因子 -α(Tumor necrosis factor-α,TNF-α)水平,美国国立卫生研究院卒中量表(National Institutes HealthStroke Scale,NIHSS)和日常生活活动能力(Activity of daily living,ADL)评分的变化和不良反应的发生情况。**结果:**治疗后,研究组总有效率显著高于对照组(91.04% vs. 78.31%,*P*<0.05);两组血小板聚集率、血小板黏附率、P 选择素、hs-CRP、IL-6、TNF-α 及 NIHSS 评分均较治疗前明显下降,且研究组以上指标均显著低于对照组,两组 ADL 评分均较治疗前显著上升,且研究组明显高于对照组(*P*<0.05)。两组治疗期间不良反应总发生率比较差异无统计学意义(*P*>0.05)。**结论:**氯吡格雷用于缺血性脑卒中的效果明显优于常规治疗,其能够有效抑制血小板活性、降低炎症因子水平、改善患者神经功能和日常生活能力。

关键词:缺血性脑卒中;氯吡格雷;血小板活性;炎症因子

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Efficacy of Clopidogrel in the Treatment of Ischemic Stroke and Its Effect on the Platelet Activity and Serum Inflammatory Factors Levels*

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ABSTRACT Objective: To evaluate the efficacy of clopidogrel in the treatment of ischemic stroke and its effect on the platelet activity and serum inflammatory factor levels. **Methods:** 150 patients with ischemic stroke who were treated from August 2016 to August 2018 in our hospital were divided into control groups (83 cases) and research group (67 cases) according to the order of admission. The control group was treated with conventional therapy, and the research group was treated with clopidogrel on the basis of control group. Then the clinical efficacy, changes of platelet activity index, serum hypersensitive c-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α(TNF-α) levels, National Institutes Health Stroke Scale (NIHSS) and the activity of daily living (ADL) scores before and after treatment and the poor reaction occurrence were compared between two groups. **Results:** After treatment, the total effective rate in the research group was significant higher than that in the control group (91.04% vs. 78.31%, *P*<0.05). The platelet aggregation rate, platelet adhesion rate, p-selectin, hs-CRP, IL-6, TNF-α and NIHSS scores in both groups were significantly decreased after treatment compared with those before treatment,the above indexes in the research group were significantly lower than those in the control group, the ADL scores of both groups were significantly higher than those before treatment, which were significantly higher in the research group than those of the control group (*P*<0.05). There was no statistically significant difference in the total incidence of adverse reactions between the two groups during treatment (*P*>0.05). **Conclusion:** The effect of clopidogrel on ischemic stroke is obviously better than that of conventional treatment, it can effectively inhibit the activity of platelets, reduce the level of inflammatory factors, and improve the neurological function and daily life ability of patients.

Key words: Ischemic stroke; Clopidogrel; Platelet activity; Inflammatory cytokines

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前言

缺血性脑卒中是脑血管疾病的主要类型之一,能够引起患者神经功能出现程度不一的缺损[1,2]。研究表明[3,4]炎症反应在缺血性脑卒中发生发展中有重要作用，和疾病严重程度密切相关,其也是动脉粥样硬化形成的主要因素,能够增加斑块不稳定性,且可导致血管平滑肌细胞的迁移及增生,使血管发生再狭窄,促进缺血性脑卒中的发生发展过程。血小板活化为缺血性脑卒中的重要生理病理改变,医学研究证实抗血小板治疗是防治缺血性脑血管病变的有效手段[5,6]。氯吡格雷可通过抑制血小板聚集避免血栓形成[7,8]。研究表明[9,10]氯吡格雷可减少动脉粥样硬化患者心血管事件发生风险,但安全性及可行性尚无明确定论。因此,本研究主要评价了氯吡格雷用于缺血性脑卒中的疗效,并探讨了其可能的作用机制。

1 资料与方法

1.1 一般资料

150 例缺血性脑卒中患者入选标准:和缺血性脑卒中诊断标准相符[11];发病至入院在 24 h 内,肝肾等主要器官无明显病变;无药物或者酒精依赖史;本研究药物禁忌证。排除标准:有手术指征;血液系统或凝血功能异常;精神系统病变;脑部其他病变;近期使用过对血小板有影响药物;接受溶栓治疗;恶性肿瘤。按入院先后顺序将患者分为对照组(83 例)和 67 例研究组(67 例)。对照组男 49 例,女 34 例;年龄 46~74 岁,平均(61.44± 8.07)岁;发病时间(14.59± 2.17)h;卒中部位:小脑 18 例、放射冠 30 例、基底部 26 例、其他 9 例;合并症:糖尿病 47 例,高脂血症 38 例，高血压 53 例。研究组男 42 例，女 25 例；年龄 45~72 岁,平均(60.85± 9.41)岁;发病时间(13.95± 2.78)h;卒中部位:小脑 16 例、放射冠 27 例、基底部 20 例、其他 4 例;合并症:糖尿病 35 例,高脂血症 29 例,高血压 40 例。两组一般资料比较差异均无统计学意义,具有可比性(P>0.05)。

1.2 治疗方法

对照组入院后立即予以基础治疗。研究组在对照组基础上联合氯吡格雷治疗,每次 75 mg 氯吡格雷(厂家:赛诺菲(杭州)制药有限公司,规格:75 mg/ 片,批号:20160112),口服,qd,持续治疗 21 d。于治疗 21 d 时评价疗效,观察药物安全性。

1.3 观察指标

1.3.1 临床疗效评价标准 NIHSS 评分降低≥ 90%,病残程度为 0 级为基本痊愈;NISSS 评分下降在 46%~90%,病残程度为 1~3 级为显著进步;NIHSS 评分下降为 18%~45%,病残程度为 4~6 级为进步;无效:NIHSS 降低≤ 17%,病残程度为 7 级即无效。基本痊愈率、显著进步率及好转率为总有效率[11]。

1.3.2 血液指标 于治疗前后抽取患者外周静脉血,将血清保存待检。采用免疫比浊法检测外周血血小板聚集率,用旋转波球法测定血小板黏附率,采用酶联免疫法检测 P 选择素、超敏-C 反应蛋白(hypersensitive c-reactive protein,hs-CP)、白介素-6(Interleukin-6,IL-6)及肿瘤坏死因子 -α(Tumor necrosis factor-α,TNF-α)水平。

1.3.3 NIHSS 及日常生活活动能力(ADL)评分 (1)于治疗前、治疗结束时进行评价,NIHSS 的分数和神经功能呈负相关。(2)ADL 分数和日常生活能力呈正相关[12,13]。

1.4 统计学分析

数据处理选用 SPSS18.0 软件包,计量资料用($\bar{x}\pm s$)表示,组间比较选用 t 检验,计数资料用[(例)%]表示,组间比较用 x^2 检验比较,以 P<0.05 表示差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后,研究组总有效率高于对照组,差异有统计学意义(91.04% vs. 78.31%,P<0.05),见表 1。

表 1 两组临床疗效的比较[例(%)]

Table 1 Comparison of the clinical efficacy between the two groups [case (%)]

Groups	n	Basic recovery	Significant progress	Progress	Ineffective	Total effective rate
Control group	83	24(28.91)	31(37.35)	10(12.05)	18(21.69)	65(78.31)
Research group	67	30(44.78)	25(37.31)	6(8.96)	6(8.96)	61(91.04)#

Note: Compared with the control group, #P<0.05.

2.2 两组治疗前后血小板活性指标的比较

治疗前,两组血小板聚集率、血小板黏附率、P 选择素比较差异无统计学意义(P>0.05);治疗后,两组血小板聚集率、血小板黏附率、P 选择素水平均较治疗前下降，且研究组以上指标均明显低于对照组(P<0.05),见表 2。

表 2 两组治疗前后血小板活性指标比较($\bar{x}\pm s$)

Table 2 Comparison of platelet activity before and after treatment between the two groups($\bar{x}\pm s$)

Groups	n	Time	Platelet aggregation rate(%)	Platelet adhesion rate (%)	P-selectin(ng/mL)
Control group	83	Before treatment	75.14± 8.04	86.35± 11.09	13.73± 1.83
		After treatment	45.28± 7.05▲	65.50± 8.64▲	10.85± 1.41▲
Research group	67	Before treatment	72.59± 9.85	83.06± 13.28	13.21± 1.30
		After treatment	39.55± 5.42▲#	50.10± 6.73▲#	8.31± 1.06▲#

Note: Compared with the control group, #P<0.05; Compared with the same group before treatment, ▲P<0.05.

2.3 两组治疗前后血清炎症因子水平的比较

治疗前，两组血清 hs-CRP、IL-6、TNF-α 水平比较差异无统计学意义(P>0.05)；治疗后，两组血清 hs-CRP、IL-6、TNF-α 水平均较治疗前显著下降，且研究组以上指标均显著低于对照组(P<0.05)，见表 3。

表 3 两组治疗前后炎症因子水平比较($\bar{x}\pm s$)

Table 3 Comparison of level of Inflammatory factor before and after treatment between the two groups($\bar{x}\pm s$)

Groups	n	Time	hs-CRP(mg/L)	IL-6(μg/L)	TNF-α(ng/L)
Control group	83	Before treatment	6.87± 0.95	18.91± 2.43	35.12± 3.21
		After treatment	3.51± 0.44▲	11.26± 1.68▲	13.28± 1.60▲
Research group	67	Before treatment	7.11± 0.86	19.67± 2.87	34.09± 3.69
		After treatment	2.96± 0.31▲#	8.15± 1.20▲#	8.10± 1.15▲#

Note: Compared with the control group, #P<0.05; Compared with the same group before treatment, ▲P<0.05.

2.4 两组治疗前后 NIHSS、ADL 评分比较

治疗前，两组 NIHSS、ADL 评分比较差异无统计学意义(P>0.05)；治疗后，两组 NIHSS 评分均下降，ADL 评分均上升，研究组变化更明显，差异有统计学意义(P<0.05)，见表 4。

表 4 两组治疗前后 NIHSS、ADL 评分比较($\bar{x}\pm s$)

Table 4 Comparison of NIHSS and ADL scores before and after treatment between the two groups($\bar{x}\pm s$)

Groups	n	Time	NIHSS(points)	ADL(points)
Control group	83	Before treatment	23.70± 3.69	41.88± 6.59
		After treatment	10.08± 1.40▲	56.03± 7.14▲
Research group	67	Before treatment	22.64± 3.11	43.71± 5.47
		After treatment	7.42± 0.96▲#	61.27± 9.03▲#

Note: Compared with the control group, #P<0.05; Compared with the same group before treatment, ▲P<0.05.

2.5 两组不良反应发生情况的比较

两组总不良反应发生率比较差异无统计学意义(P>0.05)，见表 5。

表 5 两组不良反应发生情况比较[例(%)]

Table 5 Comparison of the incidence of adverse reactions between the two groups [case (%)]

Groups	N	Gastrointestinal bleeding	Urinary bleeding	Gingival bleeding	Total adverse reaction rate
Control group	83	2(2.40)	1(1.20)	3(3.61)	6(7.22)
Research group	67	3(4.47)	2(2.98)	4(5.97)	9(13.43)

3 讨论

缺血性脑卒中的病死率较高，其临床治疗有一定难度[14,15]。目前，此类疾病的治疗仍以药物为主，其中溶栓治疗的治疗窗有一定局限性，且存在血管安全性等不足[16]。相关研究报道[17]血小板黏附在缺血性脑卒中发生中有重要作用。因此，抗血小板聚集疗法是缺血性脑卒中的重要治疗手段，但从疗效和安全性方面考虑，不同抗血小板药物在预防缺血性脑血管疾病方面的应用价值尚存争议[18]。

氯吡格雷能够一定程度的影响血小板功能，缓解疾病进展[19,20]。氯吡格雷可改善血液流变学状态，利于脑血管的扩张，改善脑部的微循环，增加脑血流量及供氧量，促进脑细胞功能的恢复[21,22]。相关研究报道[23,24]氯吡格雷治疗缺血性脑血管疾病的疗效和安全性较高。本研究结果显示氯吡格雷组治疗的缺血性脑卒中患者总有效率高于常规治疗组，说明在常规治疗基础上联合氯吡格雷能够提高此类患者的疗效，其能机制为氯吡格雷能够明显抑制血小板聚集，改善脑部血流，从而减轻神经功能损伤。

血小板活化在缺血性脑卒中发生发展中具有重要作用，血液成分及流速改变可导致血液在血管内产生血栓，引起血液循环障碍，导致组织、器官缺血、缺氧损伤[25]。血小板聚集能够引起血小板释放反应，诱导前列腺素、花生四烯酸等刺激物质分泌，导致血小板进一步聚集，形成血栓[26]。血小板聚集率及血小板黏附率为血小板功能的敏感指标，血小板聚集率上升说明形成血栓的可能性越大。P 选择素有多种生化功能，P 选择素的水平上升可提示机体处于血小板活化状态[27]。本研究结果显示患者治疗前血小板活性指标浓度较高，说明此类患者存在程度不一的血小板活化，血液黏度明显增加，患者治疗后以上指标均下降，但氯吡格雷组降低更明显，提示氯吡格雷可明显抑制机体血小板活化，降低血小板聚集率及黏附性，改善血液状态[28]。

研究表明炎症因子通过级联放大反应导致脑部血管损伤，引起微循环障碍，促进血栓形成[29]。hs-CRP 为机体典型的炎症

标志物,也是重要的急性时相蛋白,其水平上升能够影响内皮血管的扩张能力,减少一氧化氮的分泌,降低血流灌注[30]。另外,hs-CRP 又可导致粥样斑块破裂,是心血管事件的发生危险因素。IL-6 可增加血管通透性,刺激血栓形成,引起心室重构的发生。TNF-α 为机体重要的促炎性因子,可介导炎性细胞的产生聚集、黏附,引发炎症,加速细胞凋亡、坏死,还可促进血管新生[31]。本研究结果显示两组治疗后炎症因子水平均下降,氯吡格雷组下降更明显,说明氯吡格雷能够抑制炎症因子的过度分泌,维持脑细胞内环境的稳定性,减轻炎症因子对神经细胞的损伤,避免疾病发展。进一步分析,发现氯吡格雷组治疗后 NIHSS 及 ADL 评分改善更明显,说明其更能有效保护患者神经功能,改善患者日常生活能力。安全性分析显示,氯吡格雷组未明显增加出血发生率,安全性尚可。

综上所述,氯吡格雷用于缺血性脑卒中的效果明显优于常规治疗,其能够有效抑制血小板活性、降低炎症因子水平、改善患者神经功能和日常生活能力。

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